Psychopharmacology of lycanthropy

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Objective: To develop pharmacotherapies for the orphan disease lycanthropy through the pursuit of the etiologic hypothesis of a genetically determined hypersecretion of endogenous lycanthropogens.
Design: Quadruple-blind, Rubik's Cube matrix analysis.
Setting: Community practice and malpractice.
Participants: Subjects selected from inbred Ruficolla populations in Mississippi, Georgia, North Carolina and Minnesota. All who entered the study finished it.
Interventions: Chemical screening of blood samples over a hypothesized secretory cycle of lycanthropogen peaking on the day of maximum lunar illumination. Administration of synthetic lycanthropogens for behavioural testing. Experimental lycosomatization through the illumination method of Kirschbaum.
Outcome measures: None were post hoc, but some are still in hock.
Main results: Two putative lycanthropogens were isolated from the blood samples. Structural elucidation and synthesis permitted animal and clinical trials; in each of these, behavioural dysfunction was observed. Antilycanthropogen strategies included application of the principle of caged compounds and generation of a therapeutic immunoglobulin. The effects of a newly developed antihirsutic agent seemed promising. An interaction of the lycanthropogen-secretion system and ethanol was noted, which may explain behavioural aspects of alcoholism.
Conclusions: The incidence of lycomania in North America is underestimated. Soon-to-be-available pharmacotherapies should promote its early detection and treatment. Full control may depend upon advances in gene therapy.

Objectif : Mettre au point des pharmacothérapies pour la lycanthropie orpheline par l'approfondissement de l'hypothèse étiologique d'une hypersécrétion d'origine génétique de lycanthropogènes endogènes.
Conception : Analyse à quadruple insu par la matrice du cube de Rubik.
Contexte : Pratiques communautaires et douteuses.
Participants : Sujets rouquins des populations consanguines du Mississippi, de la Géorgie, de la Caroline du Nord et du Minnesota. Tous les sujets inscrits ont fini l'étude.
Interventions : Tests de dépistage chimique par prélèvements sanguins d'après l'hypothèse d'un cycle sécréteur de l'hormone lycanthropogène atteignant son apogée le jour de la luminosité lunaire maximale. Administration de lycanthropogènes synthétiques pour évaluation du comportement. Lycosomatisation expérimentale par la méthode d'irradiation de Kirschbaum.
Mesures des résultats : Aucun n'a franchi la barre, mais certains sont encore derrière les barreaux.
Résultats principaux : Deux lycanthropogènes putatifs ont été isolés des prélèvements

From the Orphan Drug Research Institute (an affiliate of Yoknapatawpha University), 666 Rowanoak Circle, Jefferson, Miss. This is the first report from the institute's Orphan Drug Development Program.

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sanguins. Par synthèse et élucidation structurale, les essais cliniques et expériences chez les animaux ont été rendus possibles; dans chacun de ces cas, nous avons observé un dysfonctionnement comportemental. Les stratégies antilycanthropogènes faisaient intervenir l'application du principe des composants emprisonnés et la génération d'une immunoglobuline thérapeutique. Les effets d'un nouvel agent antihirsutique ont semblé prometteurs. Nous avons observé une interaction entre l'éthanol et le système de sécrétion de l'hormone lycanthropogène, ce qui pourrait expliquer certains aspects comportementaux d'alcoolisme.

Conclusions : L'incidence de la lycomanie en Amérique du Nord est sous-estimée. Les pharmacothérapies qui seront bientôt disponibles devraient en favoriser la détection et le traitement hâtifs. Le contrôle complet de la maladie pourrait dépendre des progrès en thérapie génétique.

Over the last decade much attention has been focused on the orphan drug problem — those potential and needed areas of drug development that have been neglected by the research programs of the pharmaceutical industry.[1] The foremost area subject to such neglect has been that of rare diseases for which significant new drug therapies would find too small a market to enable the recovery of the high costs of drug development. Because of the intense interest in this subject by one generous philanthropist, his personally endowed Warbucks Foundation fully financed the launching of the Orphan Drug Research Institute, Jefferson, Miss., in 1984.

The first rare disease targeted by the institute's multidisciplinary research staff has been the ancient affliction of lycanthropy. Medical historians trace this condition back to the 5th century BC, when it was described among the ancient Greeks by their historian Herotodus; later, in the 1st century BC, it was described by the Roman poet Virgil. In early Europe the problem is said to have prevailed from Russia westward to the Atlantic Ocean and from Scandinavia to the Mediterranean Sea.[2] Despite the extensive, and frequently exploitive, popular literature on lycanthropy now and in medieval times, there is scant technical literature early in the era of modern medicine and psychiatry.[3-5] Sporadic cases of this apparently rare affliction continue to be noted even to the present.[6-11]

Lycanthropy, by definition, encompasses a twofold problem. The first aspect, consisting of primary lupine delusions and associated behavioural deviations (also known as lycomania), appears to be wholly a psychiatric entity, as encountered by contemporary clinicians.[6-11] The second aspect is rather a psychosomatic problem (we propose to call it lycosomatization), in which lupine facies and concordant whole-body hirsutism are the external signs that occur in combination with a lupine behavioural fixation. Because of the extreme fear, revulsion and rejection elicited by the latter symptom complex (all too frequently stigmatized by the pejorative term "werewolf") such cases have largely been missed by modern clinicians. Given the dual aspects of lycanthropy we have pursued a broad research strategy.

Background of lycomania research

An explanation for lycomania as a self-induced hallucinatory experience of medieval European practitioners of the ancient religion of Wicca has been postulated by the distinguished psychopharmacologist Siegel[12] on the basis of the anthropologic research of Harner.[13] Witches supposedly used plants containing atropine and scopolamine to induce a hallucinatory state in which the person sought to "transform" himself into a wolf or other predatory beast. Such hallucinations were facilitated by the visual and tactile stimuli arising from wearing a wolf skin as a girdle or cloak. An unintended, self-induced experience of feeling transformed into a fox is quoted by Siegel[12] from a 19th-century volume on psychology by William James. The vulpine hallucination followed the ingestion of hashish by a friend of James and was described as follows.

> I saw at least a thousand different objects. . . . There were moments of apparent lucidity. . . . I thought I was a fox and instantly I was transformed into that animal, could see my long ears and bushy tail, and by a sort of introversion felt that my complete anatomy was that of a fox. Suddenly the point of vision changed. My eyes seemed to be located at the back of my mouth; I looked out between the parted lips, saw the two rows of pointed teeth, and, closing my mouth with a snap, saw — nothing. . . . The whirling images appeared again.

Following the lead of this clear instance of hallucinogen-induced lycomania we have developed the hypothesis that spontaneous, not self-induced, lupine transformation may best be interpreted as a consequence of an endogenous hallucinogen, psychotogen or, more specifically, lycanthropogen. Although various hypothetical endogenous hallucinogens have been proposed as a cause of schizophrenia over the past four decades, none of these seemed to offer an answer to our quest, nor did they with respect to schizophrenia. Thus, a major new effort

was launched to isolate and identify the putative endogenous lycanthropogen(s).

Research protocol

Anthropochemical approaches

Obviously our first goal was to locate a suitable study population. At this point the expertise of our anthropologist colleagues became invaluable. In 1936 Linton[14] reported on a little-known tribe of US aborigines, the Nacirema, whose primeval state seemed likely to provide a favourable substrate for the manifestation of lycomania. Despite more recent reports on this population[15,16] we found that the assimilation process had progressed to such an extent that there seemed to be no pure population of Nacirema. However, we did locate several subtribes, which have retained only certain aspects of the original physiognomy, behavioural traits and culture because of interbreeding with people of western European descent.

In a recent report[17] these populations were termed the Ruficolla (singular Ruficollum). The name was coined to emphasize the ancestral trait of rufous epithelial pigmentation, which has survived only on the dorsal body surface at the level of the neck. Also, certain cultural traits have survived, although in a clearly modified form. Instead of the strong totemistic attachment to all things lupine, which characterized the pure populations,[14] we found that in many individuals there is instead a strong canine tropism. This obviously allows for greater acceptability in the prevalent contemporary North American culture.

It was convenient to obtain study subjects from populations of Ruficolla because of their propensity to converge at intervals, particularly in the autumn, on certain ancestral sites of aboriginal lupine worship such as Starkville, Miss., and Athens, Ga. Through cultural assimilation these worship festivals have actually infiltrated the culture(?) indigenous to those areas, including populaces affiliated with the so-called institutions of higher learning (Mississippi State University and University of Georgia) located there. Therefore, the Ruficolla devotional exercises toward the contemporary canine priest-warrior sect known and celebrated as "the Dogs" (sometimes spelled "Dawgs") have come to be widely accepted. An excellent study of this relationship in operation was made by A. Griffith in "What It Was, Was Football," an unpublished but widely circulated paper presented at the 1962 meeting of ASS (Academy of Sport Sociologists).

Smaller samples of subjects were obtained from two even more primitive groups of the Ruficolla, located around Raleigh, NC, and Minneapolis–Saint Paul. In the North Carolina locale there has long been a local wolfpack tradition, but only very recently was a small group identified in Minnesota that has openly associated themselves with timberwolves.

We were able to recruit from these populations a number of subjects upon whom behavioural and biochemical tests could be applied. After completing standard intelligence tests on these subjects, with considerable difficulty, we found that the intelligence level consistently measured low normal. Using a newly devised instrument to quantify a tendency for a lupine psychologic fixation we found that the scores were consistently lower for the subjects from Mississippi and Georgia than for those from Minnesota and North Carolina. Conversely, a similar instrument for detecting canine fixations gave consistently higher values for the former subjects than for the latter. Moreover, we found a lunar periodicity of the response values, the positive readings being significantly higher during the week of the full moon than at other times.

These behavioural findings led us to obtain serial blood samples for biochemical assay during the lunar cycle. Repeated high-pressure liquid chromatography profiles of plasma samples revealed an unidentified peak within 24 hours before and after a full moon. After intensive application of the latest sophisticated chemical technology we have been able to identify two similar molecules, each of which we believe is capable of acting as an endogenous lycanthropogen.[18] One of these molecules has been named lupinone, having been isolated only from the wolf-oriented Minnesota and North Carolina populations; the other, which differs by only one carbon atom in its ring structure and was found only in the plasma of subjects from the Deep South, we have named buldogone (Fig. 1).

Not surprisingly we confirmed that the plasma levels of the two lycanthropogens had a similar lunar periodicity. We recently discovered that there is a remarkable concordance between these data and those of Thakur and Sharma[19] concerning the lunar

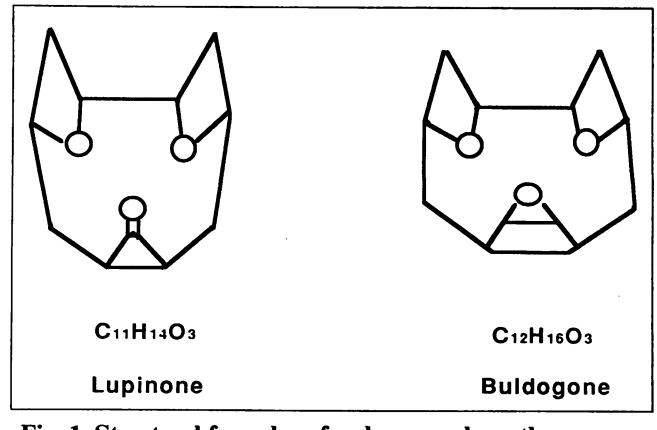

Fig. 1: Structural formulas of endogenous lycanthropogens.

periodicity of crime in India (Fig. 2). Numerous examples supporting their findings are also cited by Katzeff;[20] this suggests that our data may be generalizable in populations around the world. (We have recently been informed that evidence of similar chemobehavioural relations will soon be reported by two Canadian investigators, I. Lupino and U. Wolfish, from their work with a relic population at a remote site near Wolfville, NS [Dr. Bruce P. Squires: personal communication, 1991].)

After sufficient quantities of the newly identified compounds were synthesized, in-vivo animal testing was begun to ascertain their behavioural properties and toxic effects. First, lupinone was studied, by Lemmingson and associates,[21] appropriately in lemmings (*Lemmus lemmus*). With even the lowest dose tested (0.5 ng/g body weight) the animals showed a narrowing of the "individual sphere" of social tolerance,[21] which resulted in considerable irritability and intraspecies aggression. This may explain the irrational combativeness often observed among the Ruficolla on the occasion of their autumnal gatherings.

At higher doses, 4.9 or 9.7 pg/g body weight, lupinone was found to cause behavioural and social disruption when given to a single animal. This frequently manifested in the "mass psychosis" described previously,[21] since the untreated lemmings were found to dash madly around the test runway to escape the treated lemming. Because the latter subject's behaviour per se provided no adequate basis for the others' response we believe that the lupinone may have induced the release of a nonsexual pheromone (i.e., a fearomone). This is apparently similar to the unreasonable fear evoked in various species, including *Homo sapiens*, by the immediate presence of wolves. The behavioural response of the lemmings in this test may constitute an animal model to enable research advances in the development of a pharmacotherapy for human panic disorder.

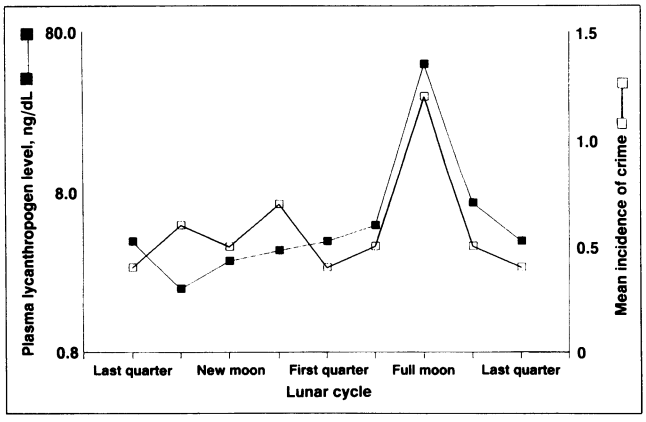

Fig. 2: Serial measures of plasma lycanthropogen levels (filled squares) across the monthly lunar period in populations of Ruficolla. The data of Thakur and Sharma[19] on the lunar periodicity of crimes in India (open squares) are replotted for comparison.

Toxicologic data for both lupinone and buldogone did not impede clinical evaluations of the compounds. Initial observations on buldogone were made in a sample of six intelligent male college graduates (from Vanderbilt University) who had no familial or personal history of mania or other psychiatric disturbance. After the oral administration of 1.0 μg of buldogone all of the subjects were found to have acute behavioural derangement rather similar to that seen in Ruficolla subjects. Saltatory movements developed in response to normally neutral auditory stimuli such as the sounding of a referee's whistle or a drum roll. Strange, unintelligible vocalizations included not only growls and barks but also a ritualistically repeated cry that could best be expressed as "Hunk Ra Down Yu Ha Ry Dawgs." A simple, seemingly clear phrase also used repetitiously was "Go-o-o Dawgs!" This thoroughly atypical behaviour, though not uncommonly observed at the Starkville and Athens sites mentioned previously, represents a type of near-mania foreign to Vanderbilt University students and alumnae. It was never noted in a control population with which Ruficolla were compared in a recent survey.[22] Similar testing of lupinone will begin shortly.

Antilycanthropogen tactics

Various approaches to the neutralization or elimination of the newly identified lycanthropogens are being pursued. Our immunopharmacology section is attempting to develop a passive immunization treatment through antibody production in vitro. This will require gene isolation and cloning for optimum success. However, interim measures with the use of antibodies against a combination of lupinone and a carrier protein have been promising. The best success occurred in the case of a carrier consisting of moose myoglobin. This molecule, to which the lupinone molecule binds with exceptional avidity, was isolated from the muscles of the hindquarters of the moose (*Alces americana*).

More immediate progress can be foreseen from our efforts to develop a drug that could neutralize the lycanthropogen molecules. We are pursuing the principle of "caged compounds,"[23] using a number of chemical exotica located in the unique, invaluable collection of Nickon and Silversmith.[24] Among the candidates culled from this source were several from their chapter on "edifice complexes" (e.g., "housane," "churchane" and the "birdcage hydrocarbon") (Fig. 3). However, the leading prospect on the basis of in-vitro interactions with buldogone is the birdcage hydrocarbon, for which we propose the new name "kennelane." It is shown in Fig. 4 with the

buldogone molecule in the desirable "caged" condition.

Background of lycosomatization research

This area of research provides even greater challenges than does the study of lycomania. Among the initial questions to be answered was the validity of the concept. Without the early, seminal work of Kirschbaum,[5] although it was little noted and too soon forgotten (the penalty of publishing in a journal not covered by *Current Contents* or *Index Medicus*), we would have been unable to substantiate the phenomenon. However, in 1971 Kirschbaum[5] defined the wavelengths of moonlight that when applied at supralunar intensity would trigger a lycanthropic transformation in otherwise unsusceptible subjects.

Unfortunately the original report did not include photographic documentation of Kirschbaum's results because of strict prohibitions by his Human Subjects Committee. However, an artist's drawing made from a photograph of one of his patients, since deceased, has now been released for publication by the family/pack of the decedent (who tragically succumbed to injuries suffered while chasing a motor vehicle) (Fig. 5). This drawing is provided in lieu of a picture of one of our subjects, all of whom are still alive, to ensure their absolute privacy.

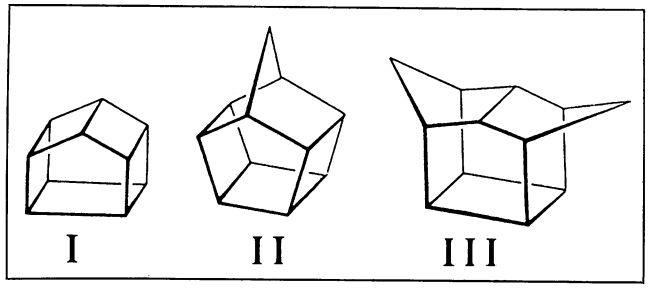

Fig. 3: Structural formulas of candidate compounds for cage complexing of the lycanthropogens: I = housane, II = churchane and III = "birdcage hydrocarbon," or kennelane. (Reproduced from Nickon and Silversmith[24] with permission.)

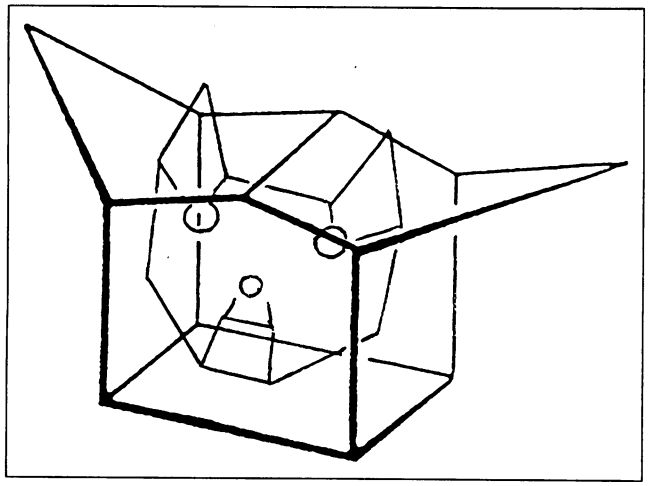

Fig. 4: Structure of kennelane with buldogone in caged conformation. (Reproduced from Nickon and Silversmith[24] with permission.)

Lycosomatization likely depends on the concurrent secretion of suprathreshold levels of both lupinone and the peptide lycanthrokinin, a second mediator, reported to be secreted by the pineal gland, that "initiates and maintains the lycanthropic process."[5] Thus, secretion of lupinone without lycanthrokinin results in only lycomania. However, Kirschbaum's highly remarkable response rate of 100% among 24 "apparently healthy male volunteers" is a finding that we have been unable to duplicate. Apparently his New Jersey population of "normal" volunteers was actually aberrant in being naturally hypersusceptible to lycanthropic transmogrification (although perhaps not so unusual for their state, where beastly behaviour is not uncommon). Nevertheless, we do have limited success to report. After 605 consecutive failures, a modified procedure has proved to be successful in our latest test, involving 10 highly selected subjects; all have shown a positive response to Kirschbaum's triple-irradiation procedure.

Our modification to the procedure consisted of testing only during a full moon, when the secretion of lupinone is at its peak. The new selection process consisted of obtaining referrals from the clients of several local shelters for battered and abused women; they were most able to direct our search to a sample of Ruficolla males having a low threshold for the display of beastly behaviour. Indeed, the plasma levels of lupinone and buldogone in these 10 subjects were elevated beyond the levels detected in our earlier unselected sample of subjects. (We are not

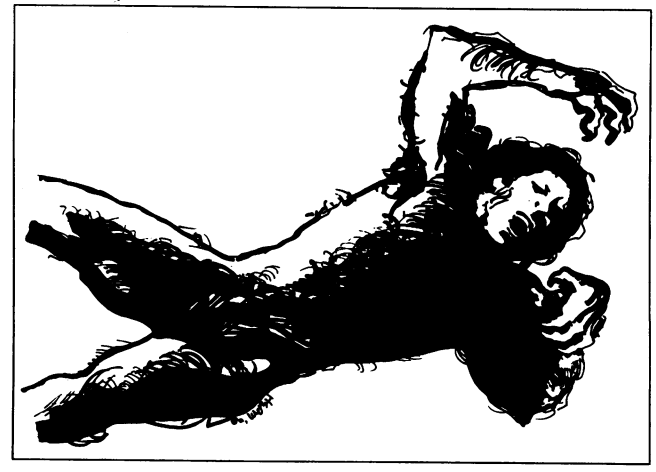

Fig. 5: Drawing from an original photograph by Kirschbaum of one of his subjects undergoing transmogrification after experimental exposure to amplified illumination at lunar wavelengths.

ignorant of the fact that women may also show this abnormality or of the need to avoid sexist bias in our choice of research subjects. However, there being no shelters for battered husbands, we have been unable to obtain referrals of a comparable sample of female subjects. We are investigating prospects among "lady" wrestlers.)

In our latest observations we discovered an association between plasma lycanthropogen and plasma ethanol levels. The 10 wife abusers showed exaggeration of an already high level of lycanthropogen when tested after the ingestion of alcohol (Fig. 6). This not only is in accord with well-known behavioural characteristics of ethanol abusers but also suggests a previously unrecognized significance of the age-old allusion to alcohol as "the hair of the dog that bit you."

An ongoing study of particular promise is one designed to find a therapy for the extreme hirsutism associated with lycanthropy. We are testing an antihirsutic agent, lidixonim, whose structure is the mirror image of the well-known compound minoxidil. It was synthesized by Smith, Bourn and Gilmour[26] with the use of a newly devised retrosynthetic technique. (This is the same Dr. Smith who did the pharmacoanthropologic research on the Nacirema cited previously.[16] He has undergone a midlife career change to resolve a long-standing problem of mass spectrometer envy.) Initial data have suggested that the compound may act as a noncompetitive antagonist at one type of lycanthrokinin receptor, located at the base of the hair follicles, on which minoxidil serves as an agonist. We suggest that these be called α-lycanthrokinin receptors, so as to leave room for designating the inevitable additional receptor subtypes to be defined by future cloners of receptor genes.

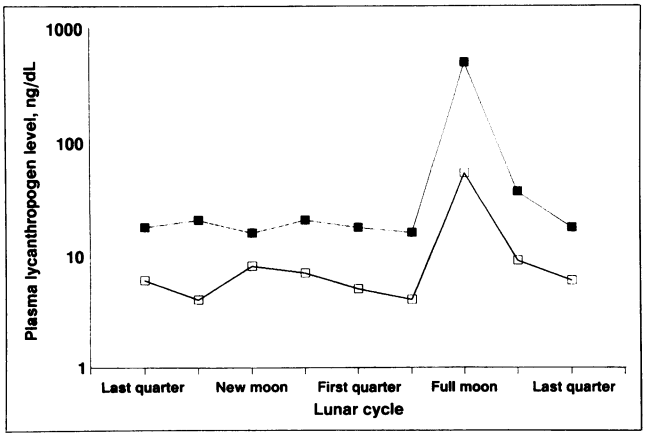

Fig. 6: Plasma lycanthropogen levels of selected Ruficolla across the lunar cycle without (open squares) and with (closed squares) prior ethanol ingestion. All the values of the former group differ significantly from those of the latter group according to Kitchen's BO test.[25]

Obviously there is a great need for further in-depth study of these relationships. The effect of ethanol on the production of lycanthropic mediators has yet to be fully characterized. We predict that an ethanol-induced elevation of the plasma lycanthropogen titre will be found to cause an increase in the synthesis and secretion of lycanthrokinin, probably through disinhibition of a normal restraining factor. G-protein activation will ensue, followed by RNA translation and triggering of the gene that controls the synthesis of that peptide.[27]

From a behavioural viewpoint these findings suggest a need to examine whether some binge drinkers' periodic absences, often attributed to their being "off somewhere drinking with their buddies," as well as their amnesic periods may actually have a more ominous explanation — namely, unrecognized (or unacknowledged) lycanthropic episodes. A Ruficolla expression possibly of interest speaks of an alcoholic bender as "prowling and howling." Also, one must consider the saying that an alcoholic is "going to the dogs" or sometimes is "howling drunk." Thus, the opportunity is great for further field research in the ethnopharmacologic relationship of alcohol and lycanthropy. Certainly for those

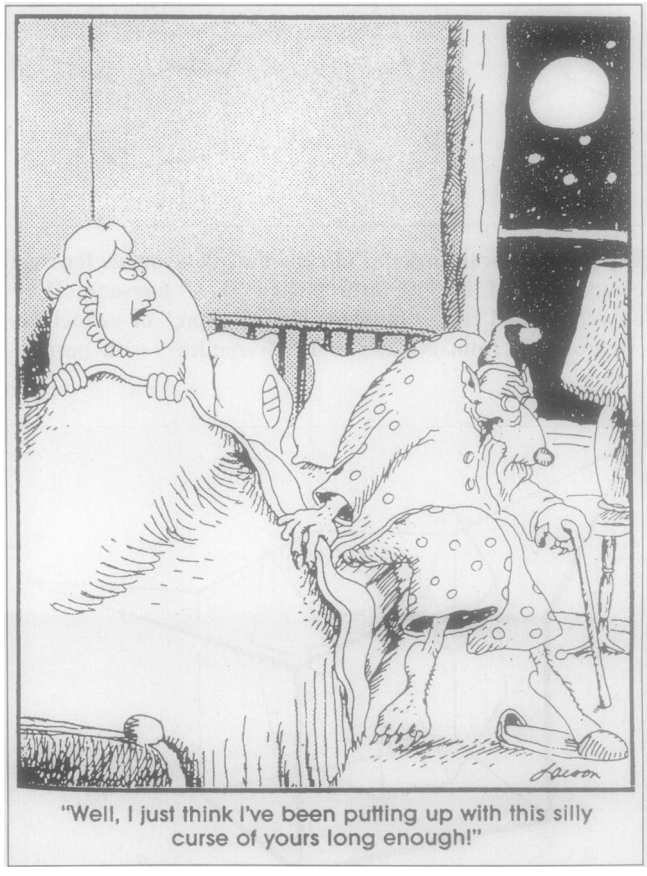

Fig. 7: Evidence of the widespread cultural recognition of the lunar role in lycanthropic transformation. (Reproduced from Gary Larson's *The Far Side* with permission from Chronicle Features, San Francisco.)

unfortunates afflicted by lycanthropy and their families a remedy for the problem is long overdue (Fig. 7).

Summary

Substantial progress toward the discovery of pharmacotherapies for lycanthropy can now be seen in the near future because of advances in immunology, biotechnology and pharmacology. Gene therapy may one day provide hope for a cure. The basic research program described in this article shows promise of providing or pointing the way to many practical benefits in the clinic and in the laboratory.

We dedicate our efforts to all those who become insomniac, or worse, during the full moon. This report commemorates the 50th anniversary of the pathfinding efforts of all who were responsible for producing *The Wolf Man*, which spawned a spate of lycanthropic cinema and perpetuated the werewolf tradition.

We thank our colleague Dr. Mickey C. Smith for offering his unfailing encouragement. We are grateful to Ms. Sharon Crandall-Couey and all the unsung members of our institute for their help in making this project a howling success. We acknowledge I.M. Kildogs, DVM, FCRAP, of the IACUC, and the Human Research Committee for their contraributions.

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